

Consommation d'alcool, syndrome métabolique et diabète dans une population à consommation moyenne d'alcool élevée

THÈSE

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***Alcohol drinking, the metabolic syndrome and diabetes in a
population with high mean alcohol consumption***

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*pour Le Doyen
de la Faculté de Biologie et de Médecine*



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Buts

Dans la littérature actuelle, peu d'études existent sur la relation entre la consommation d'alcool et le syndrome métabolique. Les quelques données disponibles sont contradictoires et très limitées chez les buveurs à haut risque. Quant au diabète, une association est connue entre la consommation à bas risque d'alcool et une prévalence diminuée de la maladie. Là encore, les données sur la consommation à haut risque sont très limitées. Par conséquent, notre but était d'étudier la relation entre la consommation d'alcool, le syndrome métabolique et le diabète dans la cohorte lausannoise (CoLaus), où la consommation moyenne d'alcool est nettement plus élevée que dans la plupart des études disponibles, notamment celles des États-Unis.

Méthodes

Nous avons analysé les données de 6172 hommes et femmes, âgés de 35 à 75 ans. La consommation d'alcool a été catégorisée en 0, 1-6, 7-13, 14-20, 21-27, 28-34 et ≥ 35 boissons par semaine ou comme non-buveurs (0), buveurs à bas risque (1-13), à risque moyen à élevé (14-34) et à très haut risque (≥ 35). Nous avons confirmé la consommation d'alcool par la γ -glutamyl transférase et la transferrine déficiente en hydrates de carbone (CDT). Après l'analyse des caractéristiques des groupes de consommateurs, nous avons utilisé des régressions multivariées pour évaluer la relation entre la consommation d'alcool, la prévalence du syndrome métabolique et du diabète ainsi que la résistance à l'insuline, déterminée par le modèle d'homéostasie de la résistance à l'insuline (HOMA-IR). Dans le modèle d'ajustement, nous avons inclus l'âge, le genre, le status tabagique, l'activité physique et le niveau de formation. Nous avons aussi comparé la relation du type d'alcool (vin, bière et spiritueux) avec le syndrome métabolique, le diabète et le HOMA-IR en testant l'hypothèse d'égalité de leurs coefficients de régression, après ajustement.

Résultats

Parmi les participants, 73% buvaient de l'alcool, 16% étant buveurs à risque moyen à élevé et 2% à risque très élevé. En analyse multivariée, la prévalence du syndrome métabolique et du diabète ainsi que le HOMA-IR moyen diminuaient avec la consommation d'alcool à bas risque et augmentaient avec la consommation à très haut risque, montrant une relation en U. La prévalence ajustée du syndrome métabolique était de 24% chez les non-buveurs, 19% chez les buveurs à bas risque ($p < 0.001$ vs. non-buveurs), 20% chez ceux à risque moyen à élevé et 29% chez ceux à très haut risque ($p = 0.005$ vs. bas risque). La prévalence ajustée du diabète était de 6.0% chez les non-buveurs, 3.6% chez les buveurs à bas risque ($p < 0.001$ vs. non-buveurs), 3.8% chez ceux à risque moyen à élevé et 6.7% chez ceux à très haut risque ($p = 0.046$ vs. bas risque). Le HOMA-IR moyen ajusté était de 2.47 chez les non-buveurs, 2.14 chez ceux à bas risque ($p < 0.001$ vs. non-buveurs), 2.27 chez ceux à risque moyen à élevé et 2.53 chez ceux à très haut risque ($p = 0.04$ vs. bas risque). Ces relations ne différaient pas selon les types de boissons.

Conclusions

La prévalence du syndrome métabolique, du diabète et le HOMA-IR baissent pour les faibles consommations d'alcool, mais augmentent à nouveau avec les plus fortes consommations, sans différence entre les types de boissons.

Original Article: Epidemiology

Alcohol drinking, the metabolic syndrome and diabetes in a population with high mean alcohol consumption

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Abstract

Aims To investigate the relationship of alcohol consumption with the metabolic syndrome and diabetes in a population-based study with high mean alcohol consumption. Few data exist on these conditions in high-risk drinkers.

Methods In 6172 adults aged 35–75 years, alcohol consumption was categorized as 0, 1–6, 7–13, 14–20, 21–27, 28–34 and ≥ 35 drinks/week or as non-drinkers (0), low-risk (1–13), medium-to-high-risk (14–34) and very-high-risk (≥ 35) drinkers. Alcohol consumption was objectively confirmed by biochemical tests. In multivariate analysis, we assessed the relationship of alcohol consumption with adjusted prevalence of the metabolic syndrome, diabetes and insulin resistance, determined with the homeostasis model assessment of insulin resistance (HOMA-IR).

Results Seventy-three per cent of participants consumed alcohol, 16% were medium-to-high-risk drinkers and 2% very-high-risk drinkers. In multivariate analysis, the prevalence of the metabolic syndrome, diabetes and mean HOMA-IR decreased with low-risk drinking and increased with high-risk drinking. Adjusted prevalence of the metabolic syndrome was 24% in non-drinkers, 19% in low-risk ($P < 0.001$ vs. non-drinkers), 20% in medium-to-high-risk and 29% in very-high-risk drinkers ($P = 0.005$ vs. low-risk). Adjusted prevalence of diabetes was 6.0% in non-drinkers, 3.6% in low-risk ($P < 0.001$ vs. non-drinkers), 3.8% in medium-to-high-risk and 6.7% in very-high-risk drinkers ($P = 0.046$ vs. low-risk). Adjusted HOMA-IR was 2.47 in non-drinkers, 2.14 in low-risk ($P < 0.001$ vs. non-drinkers), 2.27 in medium-to-high-risk and 2.53 in very-high-risk drinkers ($P = 0.04$ vs. low-risk). These relationships did not differ according to beverage types.

Conclusions Alcohol has a U-shaped relationship with the metabolic syndrome, diabetes and HOMA-IR, without differences between beverage types.

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Keywords alcohol, diabetes, insulin resistance, metabolic syndrome

Introduction

The metabolic syndrome is a common condition characterized by a constellation of metabolic risk factors, namely elevated waist circumference, triglycerides, fasting glucose, blood pressure and reduced HDL cholesterol [1]. The metabolic syndrome is associated with an increased risk of cardiovascular disease and diabetes [1]. Only a few cross-sectional studies have investigated the relationship between alcohol consumption and the metabolic syndrome, with conflicting results [2–6]. Data are particularly

limited about the association between high-risk alcohol consumption and the metabolic syndrome [4,6], as highlighted by a recent meta-analysis [7]. Theoretically, the increase of blood pressure [8] and triglycerides [9] with alcohol use suggests that the metabolic syndrome might be more prevalent in high-risk drinkers. However, HDL cholesterol also increases with alcohol consumption [10]. Among low-risk drinkers, lower waist circumference, triglycerides and blood pressure levels were observed in some studies [2,11]. Finally, very few authors have compared the influence of different beverage types on the prevalence of the metabolic syndrome [2,5,12].

The relationship between alcohol consumption and Type 2 diabetes was explored in several prospective studies, with meta-analyses showing a 30% decreased risk of diabetes in low-risk

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drinkers [13,14]. However, data are still limited and conflicting in high-risk drinkers and regarding possible differences according to beverage types [13,14]. Moreover, most epidemiological studies have found a reduced insulin resistance in low-risk drinkers, with limited and conflicting data in high-risk drinkers [15].

The aim of this study was to investigate the relationship of alcohol consumption with the prevalence of the metabolic syndrome and diabetes in a population-based study in Switzerland with high mean alcohol consumption and biochemical confirmation.

Participants and methods

Study population

This cross-sectional study examined participants from a population-based sample including 6188 Caucasian community-dwelling men and women aged 35–75 years. The details of eligibility criteria have been described previously [16,17]. Briefly, participants were identified from a random sample of all Caucasian age-eligible adults from the register of the city of Lausanne, Switzerland (117 161 inhabitants). The study included only Caucasian participants for genotyping purpose, as one of the aims of this study was to identify genetic determinants of cardiovascular risk factors. No other exclusion criteria were applied. The institutional review board in Lausanne approved the protocol; all participants gave written informed consent. They were interviewed and examined at the clinical centre in 2003–2006. Venous blood samples were collected after overnight fasting. Insulin was measured by Pathway Diagnostics (Los Angeles, CA, USA). For this analysis, we excluded 16 participants with missing data for the metabolic syndrome, giving a final sample of 6172 participants.

Alcohol consumption

As previously described [18], participants reported whether they currently used alcohol and how many standard drinks of wine, beer and spirits they had consumed in the 7 days preceding assessment, using similar methods to previous studies [11,19]. A standard drink corresponds to approximately 10–15 g of ethanol and was defined as a glass of wine, a bottle of beer or a shot of spirits [20]. Participants were categorized according to the number of standard drinks over the last week: 0, 1–6, 7–13, 14–20, 21–27, 28–34 and ≥ 35 , according to previous studies in this [18] and other populations [11,19]. Based on US and Australian guidelines [21,22] and previous definitions [20], an alternative 4-level classification was used: non-drinkers (0 drink/week), low-risk drinkers (1–13 drinks/week), medium-to-high-risk drinkers (14–34) and very-high-risk drinkers (≥ 35), the cut-off of very-high-risk drinking from the global burden of disease [23]. We used blood levels of γ -glutamyl transferase (γ GT) and carbohydrate-deficient transferrin as an objective confirmation of alcohol consumption. Carbohydrate-deficient

transferrin separation was obtained by capillary electrophoresis on a P/ACE 5510 System (Beckman Coulter Instruments, Nyon, Switzerland). We did not exclude participants with high asialotransferrin but reporting no alcohol use, as the specificity of asialotransferrin is 92% for excessive drinking [18].

Metabolic syndrome

We defined the metabolic syndrome according to the gender-specific cut-offs of the updated Adult Treatment Panel-III criteria [1] by ≥ 3 of the following measurements: waist girth ≥ 88 cm in women or ≥ 102 cm in men; triglycerides ≥ 1.7 mmol/l, use of fibrates or nicotinic acid; HDL cholesterol ≤ 1.3 mmol/l in women or ≤ 1.03 mmol/l in men, use of fibrates or nicotinic acid; blood pressure $\geq 130/85$ mmHg or use of anti-hypertensive medication; fasting glucose ≥ 5.6 mmol/l, use of oral hypoglycaemic medication or insulin. As previously reported [18], triglycerides were measured by glycerol phosphate oxidase-p-aminophenazone. HDL cholesterol was assessed by enzymatic methods (cholesterol oxidase; Roche Diagnostics GmbH, Mannheim, Germany). Blood pressure was measured by trained field investigators three times on the left arm in the seated position after ≥ 10 min of rest, using an Omron HEM-907 automated oscillometric sphygmomanometer (Omron Matsusaka Company, Kyoto, Japan) with an appropriately sized cuff. The second and third results were averaged to reduce variability [2]. Fasting blood glucose was measured by glucose dehydrogenase.

Diabetes

We defined diabetes as fasting glucose ≥ 7 mmol/l, use of oral hypoglycaemic medication or insulin [24]. We performed additional sensitivity analyses excluding self-reported Type 1 diabetes from this definition.

Insulin resistance

We evaluated insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR), defined as fasting insulin (μ U/ml) \times fasting glucose (mmol/l)/22.5 [25]. This index is proportional to insulin resistance. A score of 1 corresponds to the insulin resistance of a person < 35 years old with normal weight [15]. The HOMA-IR has been validated in normoglycaemic subjects against insulin sensitivity measured directly by the euglycaemic-hyperinsulinemic clamp technique and has been widely used in epidemiological studies [25].

Covariates

The smoking status was categorized as never, former or current smoker. Physical activity was assessed by questions on walking and other types of exercise. The socio-economic status was estimated using the education level, a validated proxy measure in Switzerland [18]. Cardiovascular disease was defined as self-

reported coronary heart disease, angina pectoris, myocardial infarction, coronary catheterization, coronary bypass, stroke or peripheral arterial disease. Weight and height were measured using Seca scale and height gauge (Seca, Reinach, Switzerland).

Statistical analysis

We conducted statistical analyses using Stata 10.1 (Stata Corp., College Station, TX, USA). First, we assessed bivariate relationships between categories of alcohol consumption and the metabolic syndrome, diabetes and other metabolic variables. Because of U-shaped relationships between alcohol use and the prevalence of the metabolic syndrome and diabetes, we also compared non-drinkers with low-risk drinkers, low-risk drinkers with very-high-risk drinkers and non-drinkers with very-high-risk drinkers. We performed multivariate analyses to assess relations between alcohol and the metabolic syndrome, diabetes and HOMA-IR, adjusting for potential confounders. For these analyses, we used logistic regression for the prevalence of the metabolic syndrome and diabetes or linear regression for HOMA-IR [18]. Odds ratios were transformed to adjusted prevalence. Similar to previous studies [2], our adjustment model included age, gender, smoking status, physical activity and education level. As previously carried out [2], we did not include BMI in this model, because BMI was highly correlated with waist circumference ($r = 0.84$, $P < 0.001$), which is a criterion of the metabolic syndrome. Furthermore, obesity may be a mediating factor of the effect of alcohol consumption on diabetes [26]. However, we performed a sensitivity analysis with further adjustment for BMI. We used similar models for other variables. Finally, we assessed the effects of the type of alcoholic beverage on the metabolic syndrome, diabetes and HOMA-IR. For this analysis, we used three variables corresponding to the consumption of wine, beer and spirits in drinks/week. We introduced them in a multivariate model testing the hypothesis of the equality of the different regression coefficients for each beverage type, as described previously [18]. As this method compares linear functions, we included only drinkers of ≥ 7 drinks/week to focus on the linear part of our results [18]. In this analysis, the adjustment model included the same above-mentioned confounders and the number of drinks of each beverage type.

Results

Baseline characteristics of the study population (Table 1)

Seventy-three per cent of participants had consumed alcohol in the last week, 55% were low-risk drinkers, 16% medium-to-high-risk drinkers and 2% very-high-risk drinkers. The gender proportions differed across drinking levels, with a minority of women in the upper categories. High levels of alcohol consumption were significantly associated with older age, male gender, current smoking, increasing γ -glutamyl transferase and carbohydrate-deficient transferrin levels. Low-risk drinkers were

significantly less physically active and more educated than non-drinkers and medium-to-high-risk drinkers (both $P < 0.001$). Wine was the most frequent beverage, but its relative consumption tended to decrease with increasing drinking levels, in favour of beer.

Metabolic variables (Table 2)

In multivariate analysis, high levels of alcohol consumption were significantly associated with increased triglycerides, HDL cholesterol, blood pressure, fasting glucose and number of metabolic criteria. Low-risk drinkers showed significantly reduced waist circumference, triglycerides, blood pressure, fasting glucose, fasting insulin and number of metabolic criteria compared with non-drinkers and very-high-risk drinkers. BMI and obesity were significantly reduced in low-risk drinkers compared with non-drinkers only. A similar result was found about the number of metabolic criteria restricted to participants with the metabolic syndrome (data not shown). Fasting blood glucose was significantly reduced in low-risk drinkers and then increased with high-risk alcohol consumption. After exclusion of 241 participants under hypoglycaemic medication, glucose was similar between non-drinkers and low-risk drinkers, and then linearly increased with high-risk alcohol consumption. Relationships of alcohol use with high triglycerides, low HDL cholesterol and high blood pressure were not altered after excluding 49 participants under fibrates or nicotinic acid, or 1094 participants under anti-hypertensive medications. Overall, the adjustment accentuated the favourable metabolic profile of low-risk drinkers and attenuated the more harmful profile at higher levels of alcohol consumption (see also Supporting Information, Table S1).

Metabolic syndrome, diabetes and HOMA-IR (Table 3)

In unadjusted analysis, the relationships of alcohol consumption with the prevalence of the metabolic syndrome or diabetes and the mean HOMA-IR followed J-shaped curves. The prevalence of the metabolic syndrome and diabetes were approximately twice higher in very-high-risk drinkers than in non-drinkers. After adjustment, low-risk drinkers had a significantly lower prevalence of the metabolic syndrome or diabetes and mean HOMA-IR compared with non-drinkers and very-high-risk drinkers. The adjusted prevalence rates in very-high-risk drinkers were higher than in non-drinkers, but not statistically different. Thus, the adjustment model transformed the J-shaped relationships into U-shaped ones (Fig. 1). Gender, smoking status and age were the most influential confounding factors in this model. The shape of these relationships did not differ by gender (P for interaction: metabolic syndrome 0.55, diabetes 0.52, HOMA-IR 0.61) and in gender-specific analyses (data not shown). Results were subject to more uncertainty for very-high-risk drinking women, because of the limited sample ($n = 13$). In this small group, no case of diabetes was detected, although with similar adjusted prevalence of the metabolic syndrome (19%) to

Table 1 Characteristics of participants according to alcohol consumption in drinks during the last 7 days

	All participants	Non-drinkers			Medium to high risk			Very high	P-value*	P for trend†
		0	1–6	7–13	14–20	21–27	28–34			
Number of participants	6172	1670 (27%)	2181 (35%)	1202 (19%)	613 (10%)	264 (4%)	116 (2%)	126 (2%)		
Age (years)	53.1 ± 10.8	52.7 ± 10.9	52.5 ± 10.7	53.5 ± 10.8	54.5 ± 10.8	54.0 ± 10.0	54.2 ± 10.2	54.4 ± 10.8	< 0.001	0.01
Women	3244 (53%)	1206 (72%)	1302 (60%)	504 (42%)	157 (26%)	49 (19%)	13 (11%)	13 (10%)	< 0.001	< 0.001
Smoking status									< 0.001	
Never	2474 (40%)	877 (53%)	937 (43%)	402 (33%)	165 (27%)	54 (21%)	18 (16%)	21 (17%)		
Former	2032 (33%)	427 (26%)	743 (34%)	454 (38%)	230 (38%)	90 (34%)	46 (40%)	42 (34%)		
Current	1665 (27%)	365 (22%)	501 (23%)	346 (29%)	218 (36%)	120 (45%)	52 (45%)	63 (50%)		
Physical activity‡ (min/week)	228 ± 243	245 ± 256	206 ± 190	225 ± 248	245 ± 287	249 ± 317	256 ± 353	237 ± 249	< 0.001	0.23
Education level (years)	13.0 ± 4.3	12.0 ± 4.3	13.5 ± 4.2	13.7 ± 4.0	12.9 ± 4.5	12.8 ± 4.0	13.6 ± 4.9	12.8 ± 4.2	< 0.001	0.28
Cardiovascular disease	429 (7%)	116 (7%)	139 (6%)	73 (6%)	52 (8%)	24 (9%)	16 (14%)	9 (7%)	0.02	0.07
Diabetes in first-degree relatives	1363 (22%)	398 (24%)	497 (23%)	240 (20%)	119 (20%)	63 (24%)	24 (21%)	22 (17%)	0.06	0.16
Percentage of beverage types										
Wine	77 ± 31	—	80 ± 33	77 ± 28	76 ± 28	68 ± 28	68 ± 28	62 ± 29	< 0.001	< 0.001
Beer	16 ± 26	—	13 ± 28	15 ± 23	18 ± 25	23 ± 27	25 ± 27	29 ± 28	< 0.001	< 0.001
Spirits	7 ± 19	—	7 ± 21	8 ± 18	6 ± 14	10 ± 16	7 ± 13	8 ± 17	0.21	0.46
Laboratory data§										
γGT¶ (U/l)	24 (23–24)	20 (19–21)	21 (20–21)	25 (24–26)	32 (30–34)	38 (35–42)	50 (43–59)	63 (55–72)	< 0.001	< 0.001
High CDT** ≥ 1.63%	366 (6%)	16 (1%)	32 (2%)	70 (6%)	87 (15%)	76 (30%)	32 (28%)	53 (46%)	< 0.001	< 0.001
High asialotransferrin** > 0%	106 (2%)	4 (<1%)	5 (<1%)	12 (1%)	28 (5%)	23 (9%)	14 (12%)	20 (17%)	< 0.001	< 0.001

The number of participants is displayed as number (percentage of all participants). Continuous variables are expressed as mean ± standard deviation and categorical variables as number (percentage in the category). Total percentages do not always match 100% because of rounding.

*P-values using ANOVA or χ^2 -test.

†P-values for trend with a test of trend across all alcohol consumption levels after linear or logistic regression.

‡Total weekly physical activity in min/week was calculated as the number of minutes of walking in a usual day + the amount of 20-min periods of intense activity in a usual week.

§γGT, γ-glutamyl transferase; CDT, carbohydrate-deficient transferrin (asialo- + disialotransferrin, available in 5905 participants).

¶Because of its skewed distribution, γGT is displayed as geometric means with 95% confidence intervals; P-values were calculated after ln-transformation.

**Normal CDT, combining asialo- and disialotransferrin, was defined as < 1.63% of total transferrin, a cut-off value including the 97.5th percentile of both abstainers and 'social drinkers' (< 30 g ethanol/day) [18]. Normal asialotransferrin was defined as 0%, because detectable values enable to identify abusive and chronic alcohol consumption [18].

Table 2 Multivariate-adjusted metabolic variables according to alcohol consumption in drinks during the last 7 days

	Non-drinkers	Low risk		Medium to high risk			Very high	P for trend*	P _{n-l} value†	P _{l-vh} value†	P _{n-vh} value†
	0	1–6	7–13	14–20	21–27	28–34	≥ 35				
Number of participants	1670 (27%)	2181 (35%)	1202 (19%)	613 (10%)	264 (4%)	116 (2%)	126 (2%)				
Weight variables											
Body mass index (kg/m ²)	26.6 ± 0.1	25.6 ± 0.1	25.4 ± 0.1	25.3 ± 0.2	25.7 ± 0.3	26.0 ± 0.4	25.9 ± 0.4	0.48	< 0.001	0.52	0.50
Obesity (BMI ≥ 30 kg/m ² , %)	20 (18–22)	13 (12–15)	11 (9–13)	13 (11–16)	14 (10–18)	12 (8–19)	15 (10–22)	0.36	< 0.001	0.45	0.46
Lipid variables											
Triglycerides (mmol/l)‡	1.22 ± 1.01	1.15 ± 1.01	1.15 ± 1.01	1.14 ± 1.02	1.28 ± 1.03	1.32 ± 1.05	1.37 ± 1.05	< 0.001	< 0.001	< 0.001	0.03
HDL cholesterol (mmol/l)	1.54 ± 0.01	1.62 ± 0.01	1.68 ± 0.01	1.74 ± 0.02	1.76 ± 0.02	1.79 ± 0.04	1.87 ± 0.03	< 0.001	< 0.001	< 0.001	< 0.001
Blood pressure variables											
Systolic (mmHg)	128.6 ± 0.4	126.7 ± 0.3	127.6 ± 0.4	131.0 ± 0.6	132.2 ± 1.0	133.4 ± 1.4	134.1 ± 1.4	< 0.001	< 0.001	< 0.001	0.001
Diastolic (mmHg)	79.1 ± 0.3	78.5 ± 0.2	78.8 ± 0.3	81.1 ± 0.4	82.5 ± 0.7	83.4 ± 1.0	82.2 ± 0.9	< 0.001	0.06	< 0.001	0.008
Glucose and insulin variables											
Fasting glucose (mmol/l)	5.58 ± 0.03	5.50 ± 0.02	5.53 ± 0.03	5.55 ± 0.05	5.62 ± 0.07	5.96 ± 0.10	5.74 ± 0.10	< 0.001	0.03	0.02	0.21
In untreated participants§	5.40 ± 0.02	5.41 ± 0.02	5.43 ± 0.02	5.47 ± 0.03	5.53 ± 0.05	5.60 ± 0.08	5.70 ± 0.07	< 0.001	0.42	< 0.001	0.001
Fasting insulin (μIU/ml)	9.39 ± 0.16	8.65 ± 0.14	7.97 ± 0.19	8.46 ± 0.27	9.08 ± 0.42	8.76 ± 0.60	9.47 ± 0.59	0.50	< 0.001	0.06	0.59
Metabolic criteria (%)											
High waist circumference¶	34 (32–37)	26 (24–28)	26 (23–28)	24 (21–28)	31 (25–37)	35 (26–45)	38 (30–48)	0.03	< 0.001	0.004	0.35
High triglycerides	26 (24–28)	22 (21–24)	21 (19–24)	22 (19–26)	29 (24–35)	26 (20–35)	32 (25–40)	0.02	0.005	0.01	0.07
Low HDL cholesterol	18 (16–20)	13 (12–15)	8 (7–10)	7 (6–10)	7 (5–11)	6 (3–12)	6 (3–10)	< 0.001	< 0.001	0.02	0.001
High blood pressure	54 (51–57)	49 (46–51)	48 (44–51)	53 (48–57)	61 (54–67)	70 (59–78)	72 (62–80)	< 0.001	0.001	< 0.001	0.002
High fasting glucose	29 (26–31)	28 (26–30)	31 (28–33)	32 (29–36)	37 (31–43)	44 (35–54)	41 (32–50)	< 0.001	0.82	0.01	0.007
Number of metabolic criteria	1.6 ± <0.1	1.4 ± <0.1	1.4 ± <0.1	1.4 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	1.9 ± 0.1	< 0.001	< 0.001	< 0.001	0.03

The adjustment model includes age, gender, smoking status, physical activity and education level. The number of participants is displayed as number (percentage in all participants). Continuous variables are expressed as mean ± standard error and categorical variables as prevalence (95% confidence interval). *P*-values comparing all consumption categories were < 0.001 for all variables, using ANOVA or χ^2 -test.

**P*-values for trend with a test of trend across all alcohol consumption levels after linear or logistic regression.

†*P*_{n-l} values compare non-drinkers with low-risk drinkers, *P*_{l-vh} low-risk with very-high-risk drinkers and *P*_{n-vh} non-drinkers with very-high-risk drinkers.

‡Triglycerides were ln-transformed because of a non-normal distribution.

§Oral hypoglycaemic medications or insulin were not used by 5931 participants.

¶Waist circumference was measured using a plastic tape, midway between the lowest rib and the iliac crest, with the subject standing at the end of a gentle expiration.

Table 3 Prevalence of the metabolic syndrome or diabetes and mean homeostasis model assessment of insulin resistance (HOMA-IR) according to alcohol consumption in drinks during the last 7 days

	Non-drinkers: 0 drink/week	Low risk: 1–13 drinks/week	Medium to high risk: 14–34 drinks/week	Very high risk: ≥ 35 drinks/week	P_{n-l} value*	P_{l-vh} value*	P_{n-vh} value*
Number of participants	1670 (27%)	3383 (55%)	993 (16%)	126 (2%)			
Metabolic syndrome (%)							
Unadjusted	24 (22–26)	21 (20–22)	28 (25–31)	40 (32–49)	0.008	< 0.001	< 0.001
Adjusted	24 (22–27)	19 (18–20)	20 (18–23)	29 (22–38)	< 0.001	0.005	0.17
Diabetes (%)							
Unadjusted	6.9 (5.8–8.2)	5.3 (4.6–6.1)	8.3 (6.7–10.1)	15.1 (9.8–22.4)	0.02	< 0.001	0.001
Adjusted	6.0 (4.9–7.3)	3.6 (3.0–4.3)	3.8 (2.9–4.9)	6.7 (4.1–10.9)	< 0.001	0.046	0.40
HOMA-IR							
Unadjusted	2.36 \pm 0.06	2.14 \pm 0.04	2.52 \pm 0.08	2.87 \pm 0.21	0.002	< 0.001	0.08
Adjusted	2.47 \pm 0.06	2.14 \pm 0.04	2.27 \pm 0.08	2.53 \pm 0.21	< 0.001	0.04	0.59

The number of participants is displayed as number (percentage of all participants). The metabolic syndrome and diabetes are expressed as prevalence (95% confidence interval) and HOMA-IR as mean \pm standard error. The adjustment model includes age, gender, smoking status, physical activity and education level. P -values comparing all consumption categories were < 0.001 for all variables, using χ^2 -test or ANOVA. * P_{n-l} values compare non-drinkers with low-risk drinkers, P_{l-vh} low-risk with very-high-risk drinkers and P_{n-vh} non-drinkers with very-high-risk drinkers.

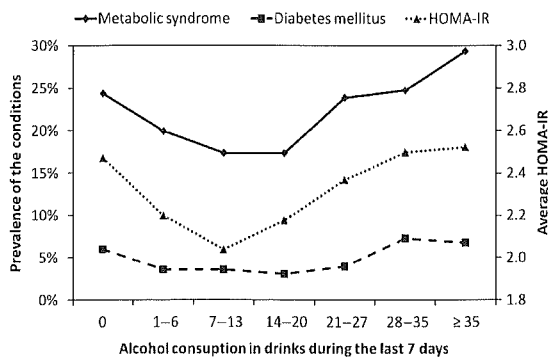


FIGURE 1 Adjusted prevalence of the metabolic syndrome or diabetes and mean homeostasis model assessment of insulin resistance (HOMA-IR) according to alcohol consumption in drinks during the last 7 days. The adjustment model includes age, gender, smoking status, physical activity and education level. The adjusted prevalence of the metabolic syndrome, diabetes and HOMA-IR was significantly reduced in drinkers of 1–13 drinks/week compared with 0 drink/week (all $P < 0.001$) and to ≥ 35 drinks/week (all $P < 0.05$), but none was significantly increased in drinkers of ≥ 35 drinks/week compared with 0 drink/week.

non-drinkers (18%) and higher than among low-risk drinkers (13%). Trends across alcohol consumption levels for drinkers of ≥ 7 drinks/week were all significant (all $P \leq 0.003$). Excluding self-reported Type 1 diabetes from the definition of diabetes did not alter the results (data not shown). Adjusting models of diabetes and HOMA-IR for BMI, waist circumference, waist-hip ratio or history of diabetes in first-degree relatives or removing diagnoses based on glucose levels only did not change the shape of these relationships (data not shown).

Beverage types

The adjusted regression coefficients of wine, beer and spirits were not significantly different for the metabolic syndrome ($P = 0.73$), diabetes ($P = 0.90$) and HOMA-IR ($P = 0.65$), after adjustment for age, gender, smoking status, physical activity, education level and the number of drinks for each beverage type (see also Supporting Information, Table S2).

Discussion

In this population-based study including a substantial proportion of high-risk drinkers, we found U-shaped relationships between alcohol use and the prevalence of the metabolic syndrome and diabetes, with reduced prevalence in low-risk drinkers and increased prevalence in very-high-risk drinkers. These relationships did not differ according to beverage types. Our results support the hypothesis of a protective effect of low-risk alcohol consumption on the metabolic syndrome and diabetes, which disappears at higher drinking levels.

For the metabolic syndrome, previous studies have found conflicting results on its relationship with alcohol, using various definitions of alcohol consumption [2–6] and including few high-risk drinkers [7]. High-risk drinkers were often included in the low-risk consumption category, attributable to insufficient numbers. For example, analyses of the US National Health and Nutrition Examination Survey (NHANES) have defined the highest consumption category as ≥ 20 drinks in the last month [2] or either ≥ 1 drink/day in the last month or ≥ 5 drinks/day ever [3]. In the Korean NHANES [4], which included drinkers up to ≥ 80 g/day, the odds ratio of the metabolic syndrome increased across drinking categories ($P < 0.005$). However, this study was restricted to Asian adults and did not confirm alcohol

consumption with laboratory tests. In a Greek study, mild-to-moderate drinkers had a reduced odds ratio of the metabolic syndrome and the opposite for heavy drinkers, defined as > 45 g/day or > 60 g at one sitting [6]. However, the adjustment model only included age, gender and smoking and regular heavy drinkers were mixed with occasional binge drinkers, again without biochemical confirmation. A recent meta-analysis found significantly reduced odds ratios of the metabolic syndrome in men drinking 0–39.9 g/day and women drinking 0–19.9 g/day [7]. No significant relationship was found at higher drinking levels, but the authors mentioned that their meta-analysis included few high-risk drinkers, potentially leading to underpowered inference about the effect of harmful drinking on the metabolic syndrome. They also found no data in women drinking > 40 g/day. Regarding differences between beverage types, previous studies have shown conflicting results, using various statistical methods [2,5,12]. Such differences might be attributed to residual confounding because of differences in lifestyle factors, such as being better educated or an ex-smoker [12].

Regarding the association between alcohol and diabetes, our results are in agreement with previous meta-analyses [13,14]. In moderate drinkers, defined as ≤ 48 g/day (~ 4 drinks/day) [13] or ≤ 30 g/day (~ 3 drinks/day) [14], the risk of diabetes was reduced by $\sim 30\%$ compared with non-drinkers. Similar to our study, Koppes *et al.* [13] have found an increased, albeit non-significant, risk of diabetes in drinkers of > 48 g/day compared with non-drinkers. However, few subjects were included in this category. Beverage types were rarely compared, with conflicting results [13]. As mentioned above for the metabolic syndrome, residual confounding for differences in lifestyle factors cannot be excluded [13].

The U-shaped relationships between alcohol consumption, metabolic syndrome and diabetes might be explained by the complex interaction of alcohol consumption with metabolic factors. Most of the previous epidemiological studies have shown a reduced insulin resistance in low-risk drinkers, but few and conflicting data exist about high-risk alcohol consumption [15]. In adjusted analyses, we found that insulin resistance also followed a U-shaped relationship with alcohol use and higher insulin resistance is associated with high-risk drinking. This may contribute to the U-shaped relationships of alcohol with the metabolic syndrome and diabetes, because insulin resistance is a central element in both conditions. Similar to our results, a favourable metabolic profile has been reported in low-risk drinkers, with significantly reduced obesity, triglycerides, blood pressure and increased HDL cholesterol [2,10,11]. However, high-risk drinking has been associated with increased blood pressure [8] and triglycerides [9], but also higher HDL cholesterol [10]. This balance between risk and protective factors among very-high-risk drinkers may explain the similar prevalence of the metabolic syndrome or diabetes in very-high-risk drinkers compared with non-drinkers. The biologic mechanisms by which chronic alcohol consumption affects metabolic factors are only partially understood. Complex effects

on glucose metabolism, lipoproteins, particularly HDL function and LDL oxidation, insulin secretion, energy balance, inflammation mediators, stress and sex hormones, vascular walls and the sympathetic nervous system have been suggested [9,15,27].

This study has several limitations. First, alcohol consumption was self reported. It might lead to a selective misclassification of high-risk drinkers as low-risk drinkers because of under-reporting, which would decrease any potential association. However, most epidemiological studies on alcohol consumption have relied on self-reported data and we used blood levels of γ -glutamyl transferase and carbohydrate-deficient transferrin as an objective confirmation of the self-reported alcohol use. To our knowledge, such a confirmation was rarely carried out in our topic with γ -glutamyl transferase [12] and never with carbohydrate-deficient transferrin. Furthermore, 1-week consumption reports are more accurate for the assessment of high-risk drinking than quantity–frequency measures [28] and are highly correlated with daily reports [28] or food–frequency questionnaires [29]. A recall period limited to 1 week may misclassify some participants usually drinking alcohol, but abstaining during this week or others drinking more in this week than usual. There is no general consensus for the definition of low-risk drinking [3,7,20]. We selected the upper limit of 14 drinks/week, based on US and Australian guidelines [21,22]. Our study neither captured drinking patterns, such as binge drinking, nor specific food parameters affecting metabolic variables, which might lead to residual confounding. Some previous studies that adjusted for food intake also found a reduced prevalence of the metabolic syndrome in low-risk drinkers [2,5]. The relatively low proportion of beer and spirit use limited the comparison of beverage types. The definition of diabetes was based on a single laboratory measurement, similar to most previous cross-sectional studies [5,6]. Finally, the cross-sectional nature of our data does not allow any definitive causal inference, but very few prospective studies on the association between alcohol consumption and the metabolic syndrome exist, particularly with sufficient number of high-risk drinkers [7]. Our study also has important strengths, such as the large, population-based sample with both genders, the high mean alcohol consumption and the objective confirmation of alcohol consumption by γ -glutamyl transferase and carbohydrate-deficient transferrin.

In conclusion, our findings indicate that alcohol has a U-shaped relationship with the metabolic syndrome, diabetes and HOMA-IR, without differences between beverage types. In future research, prospective data should confirm the relationship of alcohol consumption with the metabolic syndrome and diabetes, particularly for high-risk drinkers, as well as the impact of binge drinking. Future studies might also better quantify alcohol consumption, for example with 12-month assessments and more detailed questions [30]. Finally, the potential interactions of these relationships with other factors, such as genes, should be investigated.

Competing interests

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Unadjusted metabolic variables according to alcohol consumption in drinks during the last 7 days.

Table S2. Adjusted regression coefficients of beverage types for the metabolic syndrome, diabetes and HOMA-IR in drinkers of at least 7 drinks in the last 7 days.

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